Remarks

Claims 21, 32, 34, 35 and 38 are amended and claim 31 is cancelled. Claim 21 is amended to include the limitation from claim 31, now cancelled. Claim 21 as amended embraces increases or decreases in the level of methylation, acetylation or phosphorylation of the histone polypeptide.

Claims 132-134 are added. Support for these new claims can be found in originally filed claims 21 and 31 and in the specification at least on page 15 lines 3-21. Applicant paid for 7 excess independent claims at filing and thus no additional claims fees are required in view of these newly added claims.

Claims 21-30, 32-45 and 130-134 are pending, with claims 33, 37 and 39 presently withdrawn based on a species election. Upon allowability of the generic claim (claim 21), examination of withdrawn claims 33, 37 and 39 is requested. Applicant requests clarification regarding the withdrawn status of claim 33. Claim 33 relates to a particular bromodomain amino acid sequence. The original species election related to the amino acid sequence of a histone polypeptide from those recited in claims 37-39, of which claim 38 was elected. Accordingly, it would appear that the status of claim 33 should be "currently considered" rather than withdrawn.

No new matter has been added.

Finality of Rejection

Applicant requests reconsideration of the finality of the instant Office Action. The new rejections, particularly the new 35 U.S.C. §103(a) rejection, do not appear to have been necessitated by the prior amendment of the claims nor are they based on information submitted in an information disclosure statement filed with or after the last response. (MPEP 706.07(a).)

Reconsideration and withdrawal of finality are therefore respectfully requested.

Rejections under 35 U.S.C. §112

Claims 21-32, 34-36, 38, 40-45 and 130-131 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is rejected for not being clear regarding "the nature (of the) relationship between the amount of FRET and the level of histone "covalent" modification". The Examiner

states that claim 21 is "unclear with regards to whether FRET goes up or down with increased "covalent" modification".

Applicant respectfully traverses. The claim embraces both situations. The sample may be analyzed for the presence of compounds that covalently modify the histone polypeptide and thereby increase or decrease the level of binding between the modified histone polypeptide and the histone-modification-specific binding domain (page 14 lines 11-15). Fig. 2 illustrates that histone kinases, acetyltransferases and methyltransferases will be detected based on an increased level of FRET, while phosphatases, deacetylases and demethylases will be detected based on a decreased level of FRET. All these enzymes covalently modify the histone polypeptide.

In one instance, the claimed reporters do not undergo FRET in the absence of the biological sample. In the presence of the sample, the reporter is covalently modified (e.g., acetylated or phosphorylated), and FRET is increased relative to the starting level. In another instance, the reporters undergo FRET in the absence of the biological sample. In the presence of the sample, the reporter is covalently modified (e.g., deacetylated or dephosphorylated), and FRET is reduced relative to the starting level.

Thus, the invention intends to embrace situations in which contact with the sample results in increased or decreased FRET level relative to a level of FRET in the absence of the sample being tested. In addition, FRET levels can be compared to control samples (e.g., normal samples) and the increase or decrease in FRET level can be relative to that control level.

Claim 21 clearly and distinctly points out the subject matter claimed and reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103

U.S. Patent No. 6,465,199 in view of Akhtar et al.

Claims 21-32, 34-36, 40-45 and 130-131 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,465, 199 (Craig et al.) in view of Akhtar et al. (Nature 407:405-409, 2000). Applicant respectfully traverses the rejection in part.

Claim 21 has been amended to recite that the covalent histone modification is methylation, acetylation or phosphorylation. The claim therefore embraces analysis of biological samples based on their ability to increase or decrease methylation, acetylation or phosphorylation of a histone polypeptide.

Craig et al. relates to monitoring protein-protein interactions dependent on post-translational modification of ubiquitin, glycosyl, fatty acyl, sentrin or ADP-ribosyl groups by an enzyme. The reference discloses a method for monitoring activity of an enzyme by contacting an isolated natural binding domain with the enzyme, and then detecting binding of the isolated natural binding domain to a binding partner as a result of a post-translational modification by the enzyme. Binding interactions are detected using FRET. The reference relates to protein-protein interactions and the role of specific modifications on such interactions.

Akhtar et al. has been discussed previously. Briefly, it relates to gene dosage compensation of single male X chromosomes in Drosophila. It reports binding interactions of the histone acetyltransferase MOF chromodomain with RNA. The reference states that "chromodomains have so far not been shown to contact proteins or peptides". (See page 408, first column, last paragraph.) Binding interactions are detected using gel electrophoretic methods. The reference teachings relate to putative protein-RNA interactions.

A prima facie case of obviousness requires a motivation or suggestion to modify or combine references, a reasonable expectation of success relating to such modification or combination, and the modification or combination must provide each and every limitation of the pending claims.

A prima facie case for obviousness has not been made because all three requirements are missing. There is no motivation to combine the teachings of Craig et al. with those of Akhtar et al. because Craig et al. analyzes protein-protein interactions while Akhtar et al. speculates on RNA-protein interactions. Akhtar et al. actually teaches away from such a combination by stating that "chromodomains have so far not been shown to contact proteins or peptides". It follows in view thereof that there can be no reasonable expectation of success regarding the combination. However, even if the combination was proper (and Applicant maintains it is not), it still does not provide each and every limitation of the pending claims. The combination does not teach, inter alia, a histone-modification-specific binding domain conjugated to a histone polypeptide (claim 21), a method for analyzing phosphorylation, acetylation or methylation levels of histone polypeptides (claim 21), or a histone-modification-specific binding domain that is a 14-3-3, FHA, WW, bromodomain or chromodomain (claim 32). For these same reasons, the combination does not render obvious the newly added claims either.

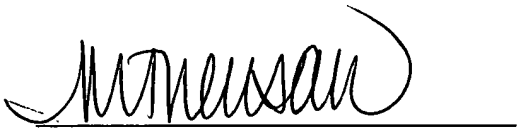
In view of the foregoing, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

A favorable action is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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